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On March 10, 2004

TOWNSEND and TOWNSEND and CREW LLP

By: Joy M. Marshall

PATENT
Attorney Docket No.: 020801-000920US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.
Ian MacLachlan, et al.	Examiner: J. Zara
Application No.: 09/243,102	Technology Center/Art Unit: 1635
Filed: February 2, 1999	AMENDMENT
For: SYSTEMIC DELIVERY OF SERUM STABLE PLASMID LIPID PARTICLES FOR CANCER THERAPY	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ian MacLachlan, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I hold a Ph.D. (1994) from the University of Alberta, and a Bachelor of Science (1988) from the University of Alberta. I am presently the Chief Scientific Officer for Protiva Biotherapeutics, Inc. (Burnaby, Canada).

My field of expertise is gene delivery and gene therapy. I have authored nineteen publications in the field of gene delivery technology, gene therapy, and molecular genetics, and am a member of the American Society of Gene Therapy and the Science Council of British Columbia, Health Technology Committee. A true copy of my *Curriculum Vitae* is attached hereto as Exhibit A.

3. The present invention is directed to methods of treating tumors in mammals by delivery of serum stable nucleic acid-lipid particles with a nucleic acid portion that is fully encapsulated within the lipid portion. The delivery of serum stable nucleic acid-lipid particles is by injection at an injection site that is distal to the tumor in the mammal. The lipid portion of the nucleic acid-lipid particle comprises a cationic lipid, a neutral lipid, and a lipid that prevents aggregation during formulation.

4. I am a named inventor on the above-referenced patent application. I have read and am familiar with the contents of the subject patent application. I have also read the Office Action received from the United States Patent and Trademark Office ("USPTO") dated September 30, 2003. It is my understanding that the Examiner is concerned that the claimed methods are not novel. Specifically, the Examiner alleges that the claims are anticipated by U.S. Patent No. 6,287,591 to Semple *et al.* ("the '591 patent"). In making this allegation, the Examiner states that the '591 patent discloses methods of treating a tumor in a mammal by distal administration of a nuclease resistant nucleic acid-lipid particle comprising a fully encapsulated nucleic acid.

5. This declaration is provided to demonstrate that the relevant disclosures in the '591 patent have a priority date that is ***after*** the date that the invention disclosed and claimed in the instant application was first disclosed and, accordingly, that the '591 patent is not prior art

and, thus, cannot anticipate the presently claimed invention. More particularly, this declaration is provided to demonstrate that the relevant disclosures of the '591 patent have a priority date of May 14, 1998, while the earliest priority date of the instant application is February 3, 1998.

6. U.S. Patent No. 6,287,591 to Semple *et al.* issued from U.S. Patent Application No. 09/078,954, filed May 14, 1998 which was a continuation-in-part of U.S. Patent Application No. 08/856,374, filed May 14, 1997. In contrast to the '591 patent, U.S. Patent Application No. 08/856,374 does not disclose or suggest methods of treating tumors in mammals by delivery of serum stable nucleic acid-lipid particles by injection at a site distal to the tumors. A perusal of the specifications of the '591 patent and U.S. Patent Application No. 08/856,374 reveals that disclosure relating to treatment of tumors by any methods, including by delivery of serum stable nucleic acid-lipid particles by injection at a site distal to the tumors was added to the continuation-in-part application filed May 14, 1998 (*see, e.g.*, '591 patent, col. 7, lines 18-56; and col. 16, lines 60-63). Therefore, the earliest priority date of the relevant disclosure of the '591 patent is May 14, 1998. For the Examiner's convenience, a copy of U.S. Patent Application No. 08/856,374 as filed with the USPTO is enclosed as Exhibit B.

7. The instant application was filed on February 2, 1999, and the earliest priority date for the application is February 3, 1998 (*i.e.*, U.S. Patent Application No. 60/072,598). U.S. Patent Application No. 60/072,598 discloses methods of treating tumors in mammals by delivery of serum stable nucleic acid-lipid particles with a nucleic acid portion that is fully encapsulated within the lipid portion. The delivery of serum stable nucleic acid-lipid particles is by injection at an injection site that is distal to the tumor in the mammal. The lipid portion of the nucleic acid-lipid particle comprises a cationic lipid, a neutral lipid, and a lipid that prevents aggregation during formulation. (*See, e.g.*, specification of U.S. Patent Application No. 60/072,598 at page 6, lines 2-3; and page 10, lines 6-9). Thus, the disclosure of the presently claimed methods of treating tumors occurred prior to May 14, 1998, *i.e.*, prior to the earliest priority date of the relevant disclosures of the '591 patent. For the Examiner's convenience, a

copy of U.S. Patent Application No. 60/072,598 as filed with the USPTO is enclosed as Exhibit C.

8. Thus, as explained in ¶¶ 6 and 7 above, the '591 patent is not prior art and, thus, cannot anticipate the presently claimed invention because the earliest priority date of the relevant disclosures of the '591 patent (*i.e.*, disclosures concerning treatment of tumors) is May 14, 1998, which is after the date on which the presently claimed invention was first disclosed.

9. The Declarant has nothing further to say.

Dated: March 7, 2004 By: _____
Ian MacLachlan, Ph.D.

60156401 v1

Curriculum Vitae

Ian MacLachlan

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Canada, V5T-4S2
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Education

May 1988 - June 1994	Ph.D. (Biochemistry), University of Alberta, Edmonton, Canada, & Department of Molecular Genetics, University of Vienna, Austria.
September 1985 - May 1988	B.Sc. (Biochemistry) University of Alberta, Edmonton, Canada.
September 1982 - May 1984	Biological Sciences University of Calgary, Calgary, Canada.

Experience

Sept 2000 – Present Protiva Biotherapeutics, Inc. 150-8900 Glenlyon Parkway Burnaby, B.C.	Chief Scientific Officer Non-viral Gene Transfer
July 1996 – Aug 2000 Inex Pharmaceuticals Corporation 100-8900 Glenlyon Parkway Burnaby, BC	Team Leader / Research Scientist Non-Viral Cancer Gene Therapy Suicide Gene Therapy, Tumor Biology Vector Development, Inducible Gene Expression
July 1994 - June 1996 Howard Hughes Medical Institute University of Michigan Ann Arbor, MI Supervisor: Dr. G.J. Nabel	Research Fellow, Department of Internal Medicine TNF Mediated Activation of NF-κB Adenoviral Gene Therapy for Restenosis Role of NF-κB in Vertebrate Development
May 1988 - June 1994 Lipid and Lipoprotein Research Group University of Alberta & Dept. of Molecular Genetics University of Vienna Supervisor: Dr. Wolfgang Schneider	Ph.D. Thesis Research: Characterization of receptor mediated uptake of riboflavin binding protein including cloning and characterization of the *rd* mutant.
January - April 1988 University of Alberta Supervisor: Dr. Wayne Anderson	Research: Computerized sequence analysis of lipoproteins, protein crystallography.
September - December 1987 University of Alberta Supervisor: Dr. Wolfgang Schneider	Research: Purification and characterization of apolipoprotein VLDL-II.

EXHIBIT A

Summer 1987 Bamfield Marine Station, Canada Supervisor: Dr. Ron Ydenberg	Research: Behavioral analysis of the polychaete, *Eudystilia vancouveri.*
May 1983 - December 1986 Canadian Hunter Exploration Ltd. Supervisor: Murray Grigg 605 5th Ave. Calgary, Alberta.	Computer programming of oil and gas reservoir simulations and data analysis tools for an oil and gas company.

Additional Training

June – September 1998 Leadership Edge Consulting	Lab-to-Leader Training Program Project Management, Coaching, Team Management
October 1997 Pape Management Consulting	Project Management Training II
February 1997 Pape Management Consulting	Project Management Training I

Awards

1995- 1998	Medical Research Council of Canada Fellowship
1993	Mary Louise Imrie Graduate Award, Faculty of Graduate Studies and Research, Vice-President (Research), University of Alberta
1992 - 1994	Austrian Fonds zur Förderung der Wissenschaftlichen Forschung (Austrian Ministry of Science Scholarship)
1989 - 1993	Heart and Stroke Foundation of Canada Research Trainee
1982	Rutherford Scholarship

Memberships and Affiliations

1998 -Present	American Society of Gene Therapy, Member
1999 -Present	Science Council of British Columbia, Health Technology Committee Member

Patents Applied For

Finn, J., MacLachlan, I., Autogene Nucleic Acids Encoding a Secretable RNA Polymerase, Filed 2001.

MacLachlan, I., Graham, R.G., Systemic Delivery of Serum Stable Plasmid Lipid Particles for Cancer Therapy, Filed 1998.

MacLachlan, I., Buchkowski, S.S., Sensitizing Cells To Compounds Using Lipid Mediated Gene and Compound Delivery, Filed 1998.

Joshi, P.J., Mortimer, I.C., Tam, P., MacLachlan, I., Graham, R.G., Combination Therapy of Nucleic Acids and Conventional Drugs, Filed 1998.

Publications

MacLachlan, I., Tam, P., Lee, D., Thompson, J., Giesbrecht, C., Lee, A., Thompson, V., Graham, R.G., A Gene Specific Increase in the Survival of Tumor Bearing Mice Following Systemic Non-viral Gene Therapy, Submitted.

Buchkowsky, S.S., MacLachlan, I., Graham, R.W., Liposomal Encapsulation of Ganciclovir Results in Improved Pharmacokinetics and Biodistribution, Submitted.

Cullis, P.R., MacLachlan, I., Fenske, D.B., Lipid Based Systems for Systemic Gene Therapy, Journal of Liposome Research, In Press.

Fenske, D.B., MacLachlan, I., Cullis, P.R., Stabilized Plasmid-Lipid Particles: a Systemic Gene Therapy Vector, Methods in Enzymology, Academic Press, San Diego, In Press.

Pampinella, F., Lecheardeur, D., Zanetti, E., MacLachlan, I., Benhaouga, M., Lukacs, G.L., Vitiello, L., Analysis of Differential Lipofection Efficiency in Primary Vs Established Myoblasts, Molecular Therapy, 5:161-169, 2002.

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Pampinella, F., Pozzobon, M., Zanetti, E., Gamba, P.G., MacLachlan, I., Cantini, M., Vitiello, L., Gene Transfer In Skeletal Muscle by Systemic Injection of DODAC Lipopolyplexes, Neurological Science, 21:S971-973, 2000.

MacLachlan, I., Cullis, P.R., Graham, R.W., Synthetic Virus Systems for Systemic Gene Therapy. In: *Gene Therapy: Therapeutic Mechanisms and Strategies*, Smyth-Templeton, N., Lasic, D.D., (Eds.) Marcel Dekker, New York, 2000.

MacLachlan, I., Cullis, P.R., Graham, R.G., Progress Towards a Synthetic Virus for Systemic Gene Therapy, Current Opinion in Molecular Therapeutics, 1: 252-249, 1999.

Mortimer, I., Tam, P., MacLachlan, I., Graham, R.W., Saravolac, E.G., Joshi, P.B., Cationic Lipid Mediated Transfection of Cells in Culture Requires Mitotic Activity, Gene Therapy, 6: 403-411, 1999.

Wheeler, J.J., Palmer, L., Ossanlou, M., MacLachlan, I., Graham, R.W., Hope, M.J., Scherrer, P., Cullis, P.R., Stabilized Plasmid Lipid Particles: Construction and Characterization, Gene Therapy, 6: 271-281, 1999.

Wu, B., Woffendin, C., MacLachlan, I., Nabel, G.J., Distinct Domains of IκB-α Inhibit Human Immunodeficiency Virus Type I Replication Through NF-κB and Rev, J. Virology, 71(4):3161-3167, 1997.

MacLachlan, I., Steyrer, E., Hermetter, A., Nimpf, J., Schneider, W. J., Molecular Characterization of Quail Apolipoprotein II: Disulphide-bond Mediated Dimerization is Not Essential For Inhibition of Lipoprotein Lipase. Biochem. J. 317: 599-604, 1996.

Elkin, R.G., MacLachlan, I., Hermann, M., Schneider, W.J., Characterization of the Japanese Quail Oocyte Receptor for Very Low Density Lipoprotein and Vitellogenin, J. Nutrition, 125: 1258 - 1266, 1995.

MacLachlan, I., Nimpf, J., Schneider, W. J., Japanese Quail Apo-VLDL-II: cDNA Sequence and Comparison to Chicken Apo-VLDL-II, a Specific Inhibitor of Lipoprotein Lipase. Atherosclerosis: 109: 62,1994.

MacLachlan, I., Schneider, W.J., Avian Riboflavin Binding Protein Binds to Lipoprotein Receptors in Association With Vitellogenin. J. Biol. Chem., 269: 24127-24132, 1994.

MacLachlan, I., Nimpf, J., White, H.B. , Schneider, W.J., Riboflavinuria in the *rd* Chicken: 5' -Splice Site Mutation in the Gene for Riboflavin Binding Protein, J. Biol. Chem. 268 : 23222-23226, 1993.

MacLachlan, I., Nimpf, J., Schneider, W.J., A Point Mutation in the Gene for Riboflavin Binding Protein Leads to Activation of Alternate Splicing Pathways Causing Riboflavinuria in the *rd* Chicken. Fed. Amer. Soc. Exper. Biol. Jour., 7: A1091, 1993.

Schneider, W.J., Vieira, A.V., MacLachlan, I., Nimpf, J., Lipoprotein Receptor Mediated Oocyte Growth. In: *Cellular Metabolism of the Arterial Wall and Central Nervous System; Selected Aspects*; Schettler, G., Greten, H. ,Habenicht , A.J.R. (Eds.) Springer-Verlag, Berlin, 1993.

Last Update : February 14, 2002

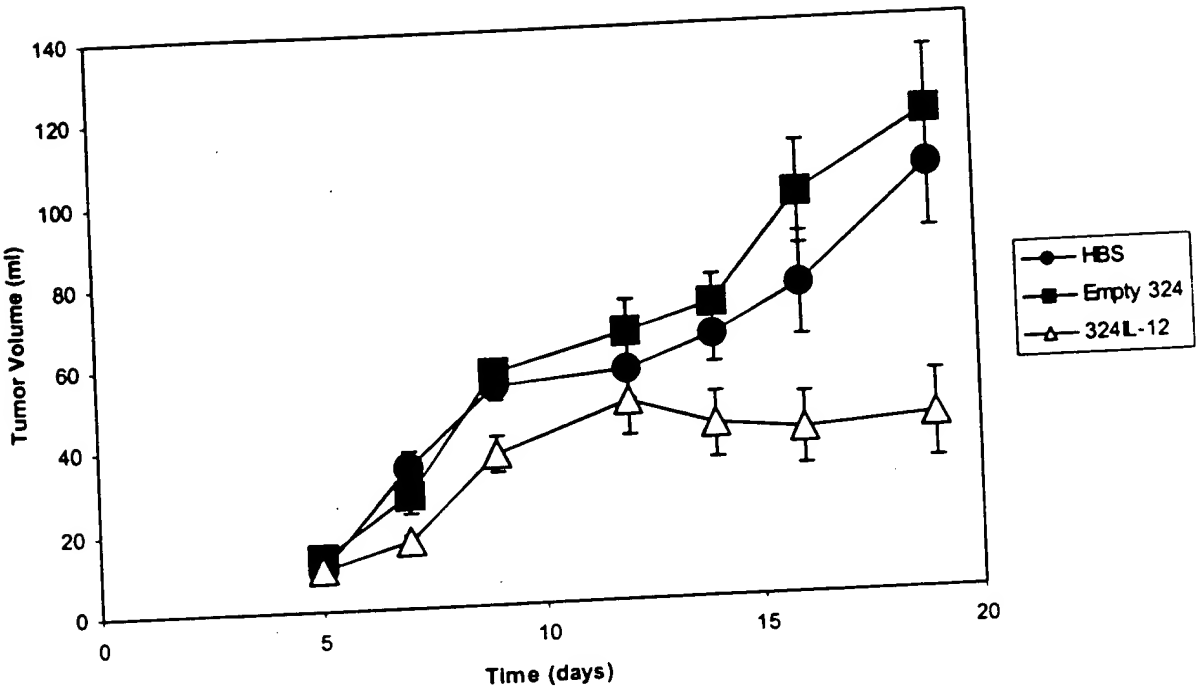
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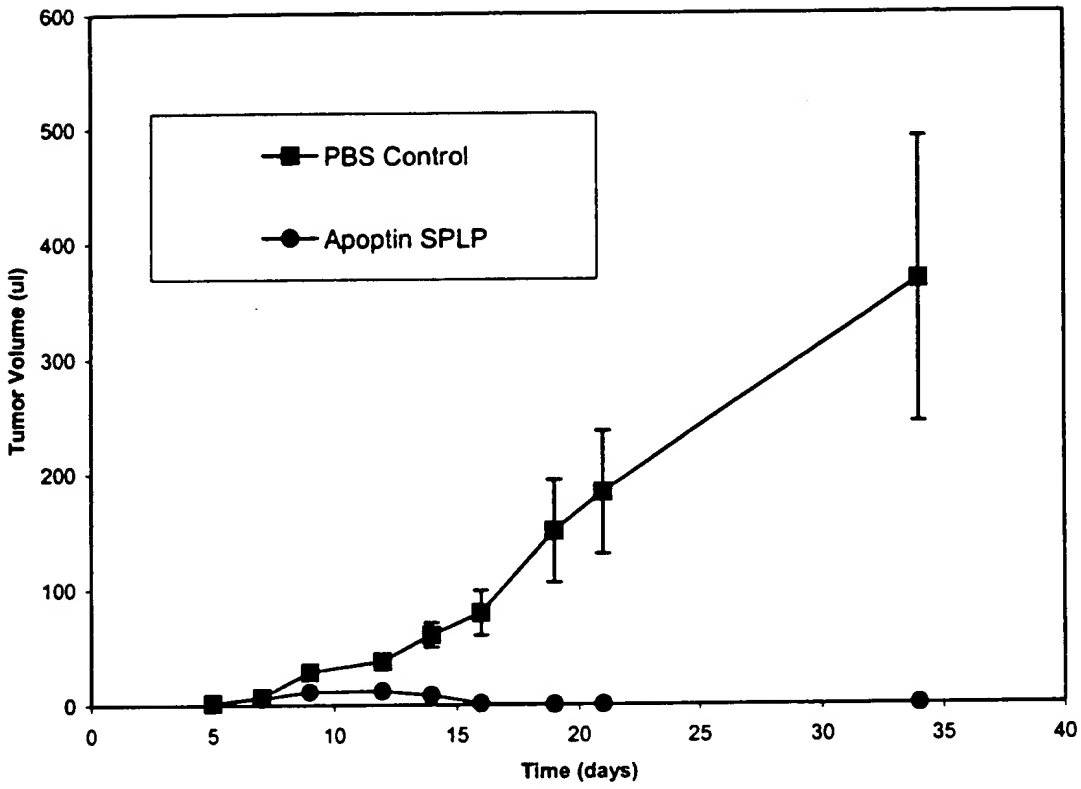
EXHIBIT B



3/4/02

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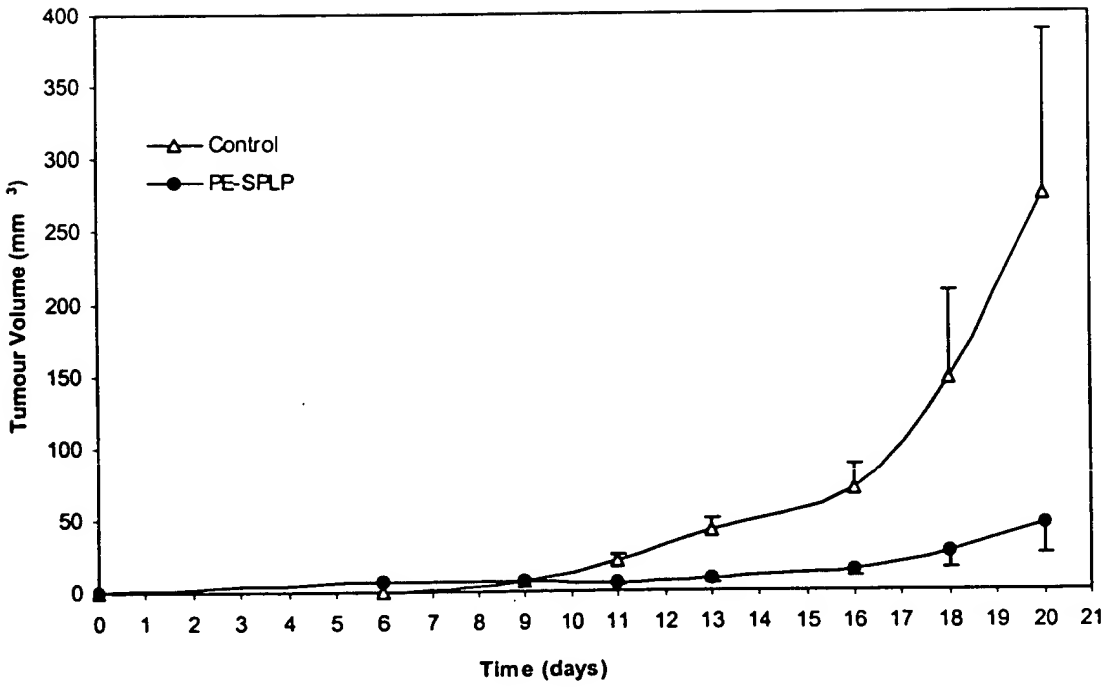

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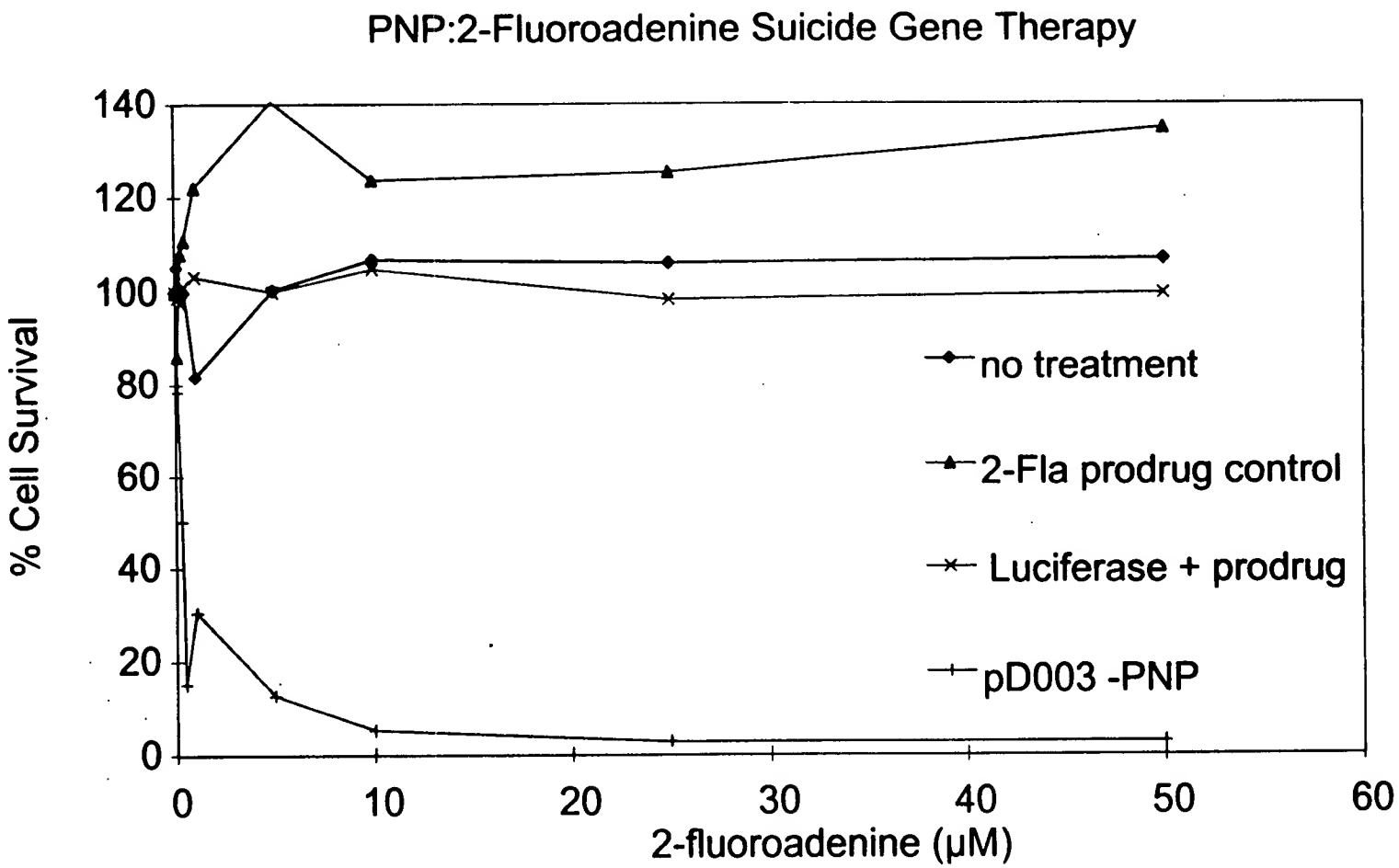
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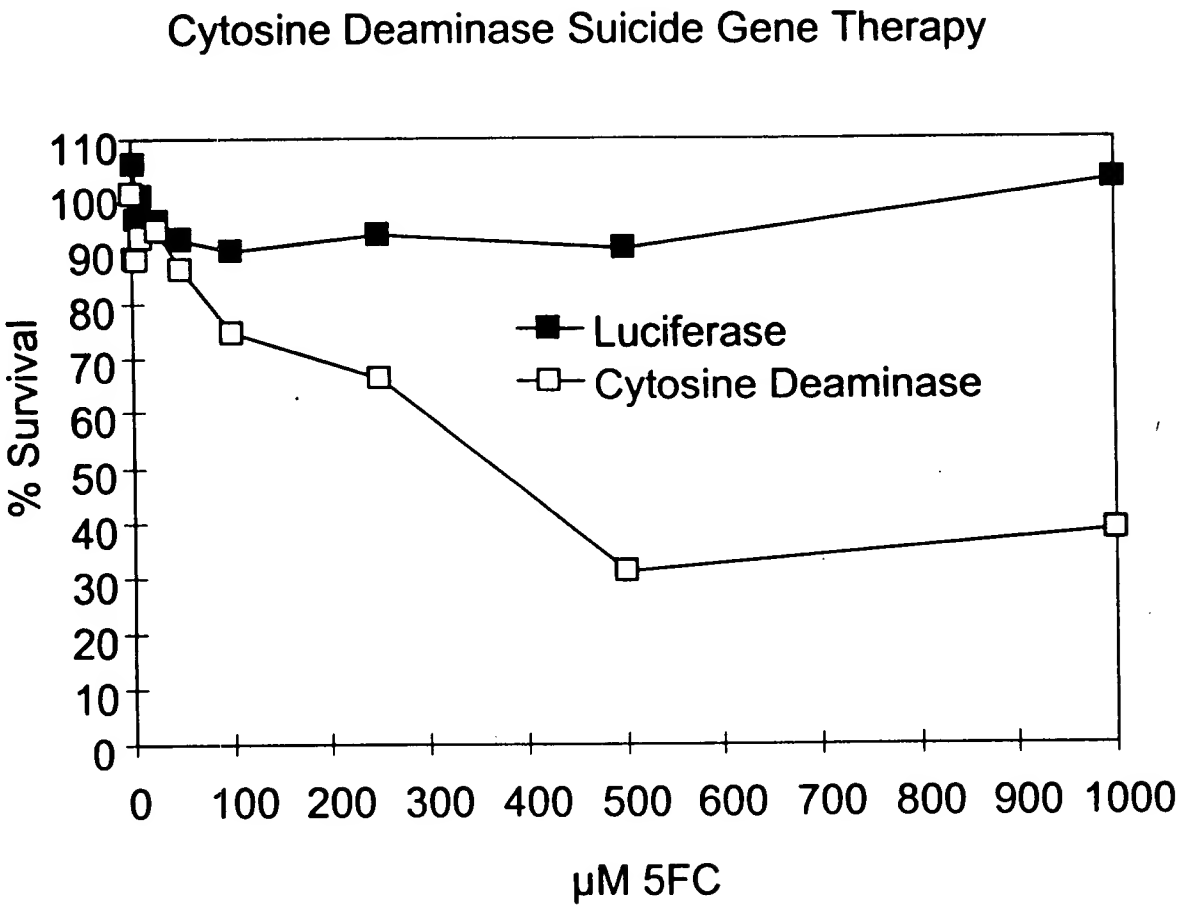
EXHIBIT E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700
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1000
µM 5FC
Luciferase
Cytosine Deaminase

EXHIBIT F